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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/675,927

09/29/2003

Payman Amiri

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03/31/2009

NOVARTIS VACCINES AND DIAGNOSTICS INC.

INTELLECTUAL PROPERTY R338

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EXAMINER

KANTAMNENI, SHOBHA

ART UNIT

PAPER NUMBER

1617

MAIL DATE

DELIVERY MODE

03/31/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/675,927	Applicant(s) AMIRI ET AL.	
	Examiner Shobha Kantamneni	Art Unit 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 January 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 75,76,78,80,82,83,87-106 and 108-112 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) NONE is/are allowed.
- 6) ☒ Claim(s) 75-76,78,80,82-83,87-106,108-112 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's amendment filed on 01/15/2009, wherein claims 75, 78, 82, have been amended.

Applicant's amendment overcomes the rejection of Claims 75-76, 78, 80, 82-83, 87-106, 108-112 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 75, 76, 78, 80, 82, 83, 87-106, 108-112 are pending, and examined herein.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 75-76, 78, 80, 82-83, 87-106, 108-112 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's amendment with respect to independent claims 75, 78, 82 has been fully considered but is deemed to insert new matter into the claims since the

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specification as originally filed does not provide support for the limitation, "R7 = H, when X2 = NR4 in formula (I)". In the original specification R7 = lower alkyl, in formula (I) (see page 4, line 14; page 7, line 3), and merely discloses R7 = H, when X1 = NR4, X2 = =N in formula (I) (see pages 4-5, 7-8, formulas II-V).

Any claim containing a limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement. See MPEP § 2163- § 2163.07(b) for a discussion of the written description requirement of 35 U.S.C. 112, first paragraph.

Specification

The amendment filed on 01/15/2009 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The amendment "R7 is hydrogen" beginning at page 4, line 14, and page 7, line 3 is not supported by the original disclosure. It is pointed out that the original specification does not recite "R7 is hydrogen" in formula (I), when X2 = NR4.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 75-76, 78, 80, 82-83, 87-106, 108-112 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a method of inhibiting Raf kinase activity in a human or animal subject suffering from a Ras/mitogen-activated protein kinase signal pathway-mediated cancer disorder selected from the group consisting of melanoma, breast cancer, prostate cancer, lung cancer, pancreatic cancer, thyroid cancer, bladder cancer, colon cancer, liver cancer, myeloid leukemia, and villous colon adenoma in a human or animal subject, comprising administering to the human or animal subject a composition comprising an amount of a specific compound represented by formula (I), does not reasonably provide enablement for inhibiting Raf kinase activity in a human or animal subject comprising administering a composition comprising **any compound** represented by formula (I). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without **undue experimentation**. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). The Nature of the Invention:

All of the rejected claims are drawn to an invention which pertains to a method of inhibiting Raf kinase activity in a human or animal subject comprising administering a composition comprising compound represented by formula (I).

(2). Breadth of the Claims:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass method of inhibiting Raf kinase activity in a human or animal subject comprising administering a composition comprising any compound encompassed by the formula illustrated by the broad structure of formula (I).

What's more, the scope of the compounds claimed to be useful for the treatment method is extremely broad.

(3). Guidance of the Specification / (4). Working Examples:

Applicant provides in the specification on pages 307-309 *in vitro* assay protocol, Raf Screening in general. The specification merely recites on page 309 "Using the procedures of Examples 1401 or 1402, the compounds of Examples 1-1094 were shown to have a raf kinase inhibitory activity at an IC₅₀ of less than 5 μ M", out of Examples 1-1094, only 2 compounds have R₇= alkyl (Example 261, R₇ =CH₃), which is

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CH3. There is no specific data i.e raf kinase inhibitory activity data, provided for any compounds of formula (I) wherein R7 is loweralkyl group. Further the assertion that the compounds exhibited raf kinase inhibitory activity at an IC₅₀ of less than 5 μ M does not guide one as to what compounds have activity and as the difference in activity of from 5 nM to 5 μ M is more than a 100 fold one would need to know the activity profile of the specific compounds tested in order to understand the scope and breadth of the invention.

There are no working examples for the method of inhibiting Raf kinase activity in a human or animal comprising administering any compounds of Formula (I).

(5). State of the Art: / (6). Predictability of the Art:

While the state of the art is relatively high with regard to a method of inhibiting Raf kinase activity in human or animal comprising administering specific compounds, the state of the art with regard to a method of inhibiting Raf kinase activity comprising administering any compounds encompassed by formula (I) is underdeveloped.

It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839 (1970). In the instant case, as discussed above, there is a vast number of compounds encompassed by the claims, the specification merely recites that the compounds of Examples 1-1094 were shown to have a raf kinase inhibitory activity at an IC₅₀ of less than 5 μ M, out of Examples 1-1094, only 2 compounds have R7= CH₃ i.e alkyl. It is pointed out that the compounds represented by formula (I) have wide variety of different

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functional groups, and will have different properties, e.g., physical, chemical, physiological effects and functions, since given the fact that any significant structural variation to a compound would be reasonably expected to alter its properties. For example, a compound with $R7=CH_3$, $Y=O$, $R1=O$, $R2=OH$ in formula (I) will have different properties such as binding abilities, solubilities, properties than a compound with $R7$ = neopentyl or pentafluoroethyl group, $Y=S$, $R1$, $R2$ form a heterocycloalkyl, and thus will have different raf kinase inhibitory activity. Furthermore, there is no evidence that the compounds actually inhibit Raf kinase activity in a human or animal. Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutical effects, side effects, and especially serious toxicity that may be generated by drug-drug interactions when and/or after administering to a host (e.g., a human) any compound represented by formula I, and other anticancer agents. See "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed., 1996), page 51 in particular. Goodman & Gilman teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right of page 51) (emphasis added). Thus, the compounds of formula (I) of the instant invention have different

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functional groups and result in different biological properties such as drug-drug interactions, formation of metabolites with different toxicities etc. Thus, the instant claimed invention as discussed above is **highly unpredictable**. The specification do not disclose which "compounds of formula (I) with R7=alkyl were tested, and do not disclose the specific Raf kinase inhibition activity of any of the compounds of formula (I).

Moreover, the standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court of *Mineral Separation v. Hyde*, 242 U.S. 262, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied.

(7). The Quantity of Experimentation Necessary:

In order to practice the claimed invention, one of skill in the art would have to first envision a compound, a dosage for each compound, an appropriate pharmaceutical carrier, the duration of treatment, route of treatment, etc. and, in the case of human treatment, an appropriate animal model system for one of the claimed compounds. One would then need to test the compound in the model system to determine whether or not the compound is effective for inhibiting Raf kinase activity, and determine whether or not the compound is effective in inhibiting Raf kinase activity in a human or animal subject suffering from a Ras/mitogen-activated protein kinase signal pathway-mediated cancer disorder selected from the group consisting of melanoma, breast cancer, prostate cancer, lung cancer, pancreatic cancer, thyroid cancer, bladder cancer, colon cancer, liver cancer, myeloid leukemia, and villous colon adenoma. One would then

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also need to test the compound in the model system for side effects and toxicity at the site of pharmacological action and the therapeutic index of the drug. Thus a person of skill in the art would have to engage in undue experimentation to test these compounds encompassed in the instant claims and their combination with other drugs to be administered to a host employed in the claimed methods of the particular treatments herein, with no assurance of success. If unsuccessful, , one of skill in the art would have to then either envision a modification of the first pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, and test the system again. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to inhibit Raf kinase activity in a human or animal subject by administration a composition comprising one of the compounds represented by formulas (I).

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, the instant specification, does not enable the skilled artisan to make and use the claimed invention commensurate in scope with these claims.

Response to Applicant's Arguments:

Applicant's arguments with respect to claim rejections have been considered but are not persuasive.

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Applicant argues that "The fact that approximately one thousand compounds within the scope of the claims show Raf kinase inhibitory activity at an IC₅₀ of less than 5 μ M provides strong evidence that the claims are enabled throughout the scope of the genus of compounds." These arguments have been considered, but not found persuasive. It is pointed out that out of Examples 1-1094, only 2 compounds have R₇=alkyl, which is CH₃. It is pointed out that the compounds represented by formula (I) have different functional groups, and will have different properties, e.g., physical, chemical, physiological effects and functions, since given the fact that any significant structural variation to a compound would be reasonably expected to alter its properties. Furthermore, there is no evidence that the compounds actually inhibit Raf kinase activity in a human or animal. For example, a compound with R₇=CH₃, Y=O, R₁=O, R₂=OH, X₂ = =N in formula (I) will have different properties such as binding abilities, solubilities, properties than a compound with R₇ = neopentyl or pentafluoroethyl group, Y=S, R₁, R₂ form a heterocycloalkyl, X₂ = =NR₄, R₄ = alkylamino, and thus will have different Raf kinase inhibitory activity. Thus, the instant claimed invention as discussed is **highly unpredictable**. The specification do not disclose which "compounds of formula (I) with R₇=alkyl, X₂ = NR₄ were tested, and do not disclose the specific Raf kinase inhibition activity of any of the compounds of formula (I).

Applicant argues that "The facts that BAY 43-9006 and the compounds of the invention share a structural feature; BAY 43-9006 has been shown to be an inhibitor of Raf 1 kinase in human clinical trials; and that the compounds of the invention have been shown to be Raf kinase inhibitors in vitro testing, all provide strong support that the

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compounds of the invention will inhibit Raf kinase activity in a human or animals." These arguments have been considered, but not found persuasive. It is pointed out that BAY 43-9006, and instant compounds of formula (I) have different structures and will have different properties. BAY 43-9006 has a pyridine ring, and the instant compounds are benzoimidazole compounds which are structurally very different and will have different properties such as binding abilities, solubilities, and Raf kinase activities. Thus, BAY 43-9006 has been shown to be an inhibitor of Raf 1 kinase in human clinical trials does not provide support that the compounds of the invention will inhibit Raf kinase activity in a human or animals, since they are structurally different compounds.

Applicant argues that "The Examiner also comments on the unpredictability of therapeutic effects, side effects, and serious toxicity that may be generated by drug-drug interactions if compounds of the invention were to be administered with other anticancer agents. It is improper for the Examiner to base his rejections on purported safety issues." These arguments have been considered. It is pointed out that one of skill in the art would recognize that it is highly unpredictable in regard to therapeutical effects i.e Raf kinase activity in a human due to drug-drug interactions that may be generated when and/or after administering to a host (e.g., a human) any compound represented by formula I, and other anticancer agents. See "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed., 1996), page 51 in particular. Goodman & Gilman teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse

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drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed". Thus, the instant claimed invention as discussed above is **highly unpredictable**.

Applicant arguments with respect to Example J have been considered, but not found persuasive. It is pointed that applicant has not provided any *in vivo* data for any of the instant compounds of formula (I). Accordingly, there is no evidence that the compounds actually inhibit Raf kinase activity in a human or animal. As discussed above, it would require undue, unpredictable experimentation to practice the claimed invention to inhibit Raf kinase activity in a human or animal subject by administration a composition comprising one of the compounds represented by formulas (I).

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period, will expire on the date the advisory action is mailed, and any

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extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shobha Kantamneni whose telephone number is 571-272-2930. The examiner can normally be reached on Monday-Friday, 8am-4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, Ph.D can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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